Case reports

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Benzylpenicillin-induced leucopenia

Complication of treatment of bacterial endocarditis

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A case of leucopenia resulting from treatment with benzylpenicillin is described. In common with the five previously reported cases of penicillin-induced leucopenia, the patient was receiving high dosage therapy for the treatment of bacterial endocarditis. The leucopenia, which was accompanied by a fever and maculopapular rash, was reversed on discontinuing treatment.

In the majority of cases of bacterial endocarditis the causal organism is sensitive to benzylpenicillin (Finland and Barnes, 1970). Thus this antibiotic is widely used in the treatment of endocarditis and its curative value and low toxicity are well proved. It is common for benzylpenicillin to be given in large doses by the intravenous route for a period of weeks to ensure eradication of the infection.

Toxic effects of benzylpenicillin are rare and mainly confined to the central nervous system, but hypersensitivity is more common, ranging from a mild urticarial reaction to fatal anaphylaxis. Haematological manifestations of hypersensitivity to penicillin G are rare though a haemolytic anaemia with positive Coombs test has been reported with high dosage intravenous therapy (Petz and Fudenberg, 1966; White *et al.*, 1968) and intramuscular treatment (Rossiter, Gray, and Shinton, 1968). Leucopenia is another rare manifestation of hypersensitivity, only five cases having previously been recorded.

Case report

A 39-year-old woman presented with a 4-month history of non-productive cough, malaise, joint pain, and night sweats. There was no past history of rheumatic fever, but at the age of 29 a diagnosis of mitral regurgitation was made. Over the subsequent 10 years she received intermittent courses of antibiotic therapy, including phenoxymethylpenicillin, for recurrent chest infections. Four months before the onset of the present illness a small mouth ulcer had developed and healed spontaneously, and one month before symptoms developed she broke a tooth but did not seek dental treatment.

On admission to hospital her temperature was 38·5°C. There were Osler's nodes present on three digits but there were no splinter haemorrhages and the spleen was not palpable. The only abnormal physical sign in the cardiovascular system was a loud pansystolic murmur at the apex. There was no diastolic murmur. The chest *x*-ray was normal, as was the electrocardiogram.

A clinical diagnosis of mild mitral regurgitation and infective endocarditis was made and confirmed by the isolation of a micro-aerophilic non-haemolytic streptococcus from four separate blood cultures. The organism was sensitive *in vitro* to penicillin, and several other antibiotics. Haematological findings were as follows: haemoglobin 9·7 g/100 ml, mean corpuscular volume 78 μ^3, mean corpuscular haemoglobin concentration 33 per cent, reticulocyte count 2 per cent, white cells 4400/mm^3, neutrophils 74 per cent, lymphocytes 22 per cent, myelocytes 4 per cent, platelets 185,000/mm^3. The Coombs test was negative; the blood urea, electrolytes, plasma proteins, and hepatic function tests were normal, and latex and antinuclear factor tests were negative.

Treatment was begun with intravenous benzylpenicillin 20 mega units daily and reduced after one week to 12 mega units daily. At the end of the first week of treatment (Fig.) the temperature had fallen to normal and the white cell count was 5900/mm^3. Fever developed again on the seventeenth day. Treatment was continued while investigation of the cause of the fever was carried out. Repeated blood cultures and urine cultures were negative. On the 21st day the haemoglobin level had fallen to 8·6 g/100 ml with a reticulocyte count of less than 1 per cent and a white cell count of 2100/mm^3. On the 23rd day a generalized maculopapular rash appeared and the

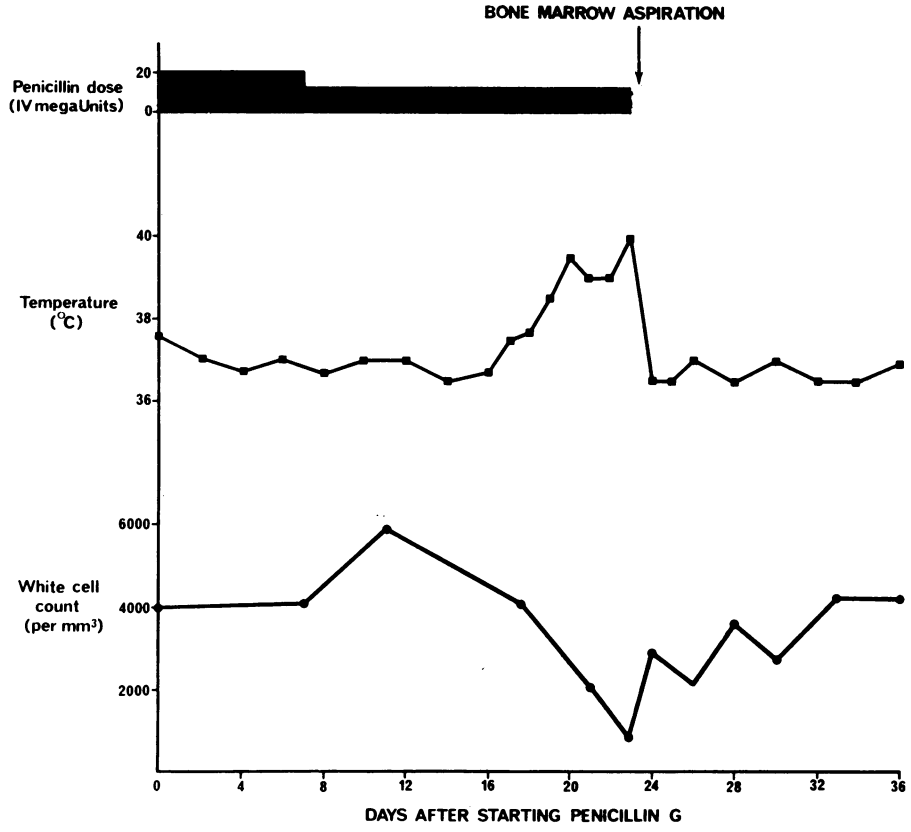

FIG. *Temperature and white cell count during and after treatment with benzylpenicillin.*

white cell count fell to 900/mm³, with neutrophils 9 per cent, lymphocytes 34 per cent, monocytes 51 per cent, eosinophils 2 per cent, and metamyelocytes 4 per cent. The platelet count remained normal and the Coombs test was again negative.

Leucocyte antibodies could not be demonstrated by saline agglutination at 4°C, 20°C, and 37°C or by a complement-fixation test. A lymphocytotoxic test was negative against 10 lymphocyte samples. No platelet antibodies could be demonstrated by agglutination, complement fixation, or Coombs consumption methods.

A bone marrow aspiration revealed increased cellularity but with reduced erythropoiesis; megakaryocytes were present in normal numbers but granulopoiesis was conspicuously increased with myelocytes and promyelocytes predominating. Only very scanty mature forms were seen.

Treatment with benzylpenicillin was discontinued on the twenty-third day with a rapid fall in the temperature. The white cell count rose to 3600/mm³ within 5 days (Fig.). Further antibiotics were not given and the patient made a rapid recovery. On discharge from hospital there was no clinical evidence of the original infection, the signs of slight mitral regurgitation were unchanged, and the blood count was normal.

During the period of treatment with benzylpenicillin the only other drugs given were paracetamol and nitrazepam.

Discussion

Leucopenia due to benzylpenicillin therapy is a rare event and only 5 previous cases have been reported (Petz and Fudenberg, 1966; White *et al.*, 1968; Forshaw, 1968; Rossiter *et al.*, 1968; Joorabchi and Kohout, 1973). In each case patients received high dosage therapy for the treatment of bacterial endocarditis, 4 of them intravenously and 1 intramuscularly (Table). While it is possible that a disturbance of immunological mechanisms related to the infection may account for this similarity, it seems more likely that the common factor is high dosage parenteral therapy.

Haemolytic anaemia occurs only with high dosage therapy probably because of the necessity for the red

TABLE *Details of reported cases of penicillin-induced leucopenia*

	Route + dose	*Coombs and anti-penicillin antibodies*	*Reversibility*	*Rash*	*Peripheral white cell count*		*Platelets*	*Bone marrow*
Present case	20 mega units per day I/V	Negative	Yes	Yes	Total count Neutrophils Mononuclear	900 9% 85%	Normal	Cellularity increased; erythropoiesis decreased; granulopoiesis increased; few mature forms in white cell series
White *et al.* (1968)	20 mega units per day I/V	Positive	Yes	Yes	Total count No differential	3200	Not known	Erythropoiesis increased; pronounced left shift in granulopoiesis
Forshaw (1968)	16 mega units per day I/V	Negative	Yes	Not stated	Total count Neutrophils Lymphocytes	950 9% 88%	Normal	Cellularity increased; erythropoiesis normal; no mature granulocytes; plentiful myelocytes
Petz and Fudenberg (1966)	100 mega units per day I/V	Positive	Yes	Yes	Total count Neutrophils Lymphocytes	1600 11% 63%	Not known	Cellularity normal; depression of granulocyte precursors
Joorabchi and Kohout (1973)	20 mega units per day I/V	Negative	Yes	Yes	Total count Neutrophils	2300 7%	Low	Hypercellularity with predominance of mature forms in myeloid and erythroid series; 'postmaturation arrest'
Rossiter *et al.* (1968)	8 mega units per day I/M	Positive	Yes	No	Total count Neutrophils	2300 2%	Low	Erythropoiesis normal; no mature granulocytes

cells to be coated with penicillin (Petz and Fudenberg, 1966) in the presence of circulating IgG penicillin antibodies (White *et al.*, 1968). Of the 6 reported cases of leucopenia, 3 also had Coombs positive haemolytic anaemia and in these cases penicillin antibodies were demonstrated. The leucopenia may, therefore, be the result of immunologically determined peripheral destruction of white cells (Forshaw, 1968). No leucocyte antibodies were seen in the present case but the test system did not include benzylpenicillin. Nevertheless leucocyte antibodies have been demonstrated by similar techniques in the absence of penicillin in a previous case (Rossiter *et al.*, 1968). Alternatively a disturbance in the production of white cells in the bone marrow may be responsible for the leucopenia and the findings in the present case are compatible with this explanation. However, the appearances of the bone marrow in the reported cases are variable both with respect to the red and white cell series. In 2 cases erythropoiesis was increased, in 2 it was normal, and in 1 it was reduced. Granulopoiesis was active with a predominance of immature forms in 4 cases, but in 1 patient cellularity was normal though granulocyte precursors were depressed and in the other case there was a 'postmaturation' arrest.

The diagnosis of antibiotic hypersensitivity may be difficult during the treatment of bacterial endocarditis as the differential diagnosis must include reactivation of the infection or unmasking of a second, resistant, infecting organism. The development of a maculopapular erythematous rash may be useful in the diagnosis of penicillin allergy and occurred in 4 of the 6 cases with leucopenia. In the present case the late development of the rash led to continuation of antibiotic therapy while further in-

vestigation of the recurrent pyrexia was performed.

We have not felt it necessary or desirable to subject this patient to an intravenous challenge dose of benzylpenicillin, though it has been suggested that the IgG antibodies involved in the leucopenic reaction act as blocking antibodies to IgE induced anaphylaxis (Levine, 1966) and such a challenge has been performed in 2 previous cases (Petz and Fudenberg, 1966; Joorabchi and Kohout, 1973). Nevertheless, even a reversible leucopenia induced by a challenge dose may have serious consequences particularly in patients with valvar disease.

Leucopenia is a rare manifestation of hypersensitivity to benzylpenicillin which may occur in patients receiving high dosage parenteral therapy in the treatment of bacterial endocarditis.

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